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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,577	07/11/2003	Blaise Bossy	10225-042001	3790
20985	7590	07/05/2006	EXAMINER	
FISH & RICHARDSON, PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022				CANELLA, KAREN A
			ART UNIT	PAPER NUMBER
			1643	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,577	BOSSY ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-18 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date 1/26/2004.
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

DETAILED ACTION

Claims 1-18 are pending and examined on the merits/

Priority

Acknowledgement is made of applicants claim to an earlier effective filing date through dependence on applications 09/619,033, filed 7/19/2000; 60/144, 529, filed 7/19/2000; 10/081,714, filed 2/20/2000; 09/344,308, filed 6/24/1999; and 60/129,384, filed 4/13/1999.

Upon review of each of these applications, it is concluded that said applications do not provide support for the instant invention. The instant invention is drawn to a method for identifying “rare events” in a biological sample, which is broader in scope than the methods contemplated in the ‘033 and ‘529 applications which were confined to methods of obtaining or enriching a composition with cells having a proliferative disorder. The instant method claims is reliant upon a “rare event” which can encompass such occurrences as detecting a fetal cell in maternal blood, detecting a stem cell in a biological sample comprising sample comprising somatic cells, detecting myocardial cells in peripheral blood, detecting a rare infected cell or rare pathogen in a biological sample. It is concluded that due to the enlargement of the breath of the claims to encompass the detection of cells beyond those cells having a proliferative disorder, that the prior applications fail to provide an adequate description of the claimed invention. Therefore, the instant claims are afforded the priority date of the instant filing date, 7/11/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. claim 15 is vague and indefinite in the recitation of “dye such as eosin...”. It is unclear whether eosin or Kleihauer-Betke are required limitations of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6-13, 17 and 18 are rejected under 35 U.S.C. 102(e) and 35 U.S.C. 102(a) as being anticipated by O'Hara et al (WO 03/035895).

Claim 1 is drawn to a method for identifying rare events in a biological sample, comprising: obtaining a source of cells; contacting the source with a binding agent specific for a cell specific marker associated with a rare event wherein the binding agent is bound to a magnetic bead and wherein the binding agent binds to cells in the source expressing the cell specific marker; separating cells bound by the binding agent from the source thereby obtaining a sub-population of cells enriched for the cell specific marker associated with the rare event; placing the enriched sample on a substrate; automatically scanning the substrate at a plurality of coordinates; automatically obtaining a plurality of images at locations on the substrate that comprise the enriched sample; and processing the plurality of image to identify the rare event. Claim 2 embodies the method of claim 1, wherein the binding agent is an antibody. Claim 3

embodies the method of claim 1, wherein the sub-population is enriched for carcinoma cells. Claim 4 embodies the method of claim 1, wherein the separating is done by positive selection. Claim 6 embodies the method of claim 2, wherein the antibody is monoclonal or polyclonal. Claim 7 embodies the method of claim 2, wherein the antibody recognizes an epithelial marker. Claim 8 embodies the method of claim 2, wherein the antibody is selected to avoid cross reactivity with the beads. Claim 9 embodies the method of claim 3, wherein the carcinoma cells are from peripheral blood. Claim 10 embodies the method of claim 1, further comprising: (a) automatically identifying a coordinate of the rare event; and (b) automatically acquiring an image of the rare event, at the location coordinates. Claim 11 embodies the method of claim 1, wherein the rare event is detected by immunohistochemistry. Claim 12 embodies the method of method of claim 1, wherein the rare event is detected by in situ hybridization. Claim 13 embodies the method of claim 1, wherein the rare event is detected by a stain. Claim 17 embodies the method of claim 1, wherein the cell specific marker is detected by immunohistochemistry, in situ hybridization, staining or a combination thereof. Claim 18 embodies the method of claim 1, wherein the image is a digital image.

O'Hara et al disclose a method of diagnosing the presence and the severity of a disease comprising detecting the presence of circulating cancer cells (page 15, second full paragraph and page 16, first paragraph). O'Hara et al disclose that cancers cells of epithelial origin can be isolated from patient blood or bone marrow sample by using immunomagnetic particle which bind to cancer cells (page 5, lines 5-7). O'Hara et al teach that the immunomagnetic particles comprise an EPCAM ferrofluid which comprise a monoclonal antibody which reacts with EpCAM on epithelial cells (page 40, lines 1-4), thus fulfilling the specific embodiment of an antibody which fulfills the specific embodiments of claims 6 and 7 . O'Hara et al disclose in situ hybridization combined with immunohistochemistry for the detection of circulating cancer cells (page 28, lines 17-21, page 17, lines 21-25 and page 20, third paragraph), which fulfills the specific embodiments of claim 11, 12, 13 and 15. O'Hara et al disclose the detection of mRNA can proceed with automation (page 28, lines 6-10), thus fulfilling the specific embodiment of claim 10. O'Hara et al disclose multiparameter flow cytometry, and image analysis (page 1 under "Field of the Invention") which fulfills the specific ;limitations of claim 18 requiring a digital image. Further, it would have been inherent in the method of O'Hara et al that the anti-

EpCAM antibody was selected to avoid cross-reactivity with the beads in order that the antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells (page 18, third full paragraph).

Claims 1-4, 6-14, 16, 17 and 18 are rejected under 35 U.S.C. 102(e) and 35 U.S.C. 102(a) as being anticipated by Pachmann et al (US 2003/0017514).

Claim 14 embodies the method of claim 13 wherein the stain is a nucleic acid dye selected from a group including propidium iodide. Claim 16 embodies the method of claim 1 wherein the cell specific marker is detected by a nuclear stain and a counter stain.

Pachmann et al disclose a method for detecting and isolating vital tumor cells in body fluids, in particular peripheral blood (paragraph 0017) comprising using anti epithelial antibodies bound to magnetic particles, wherein the tumor cells are additionally labeled by an anti-epithelial antibody bound to a flurochrome (claims 1-10). Pachmann et al disclose that the isolated tumor cells can be placed on a solid support and scanned by a laser(paragraph 0023). Packman et al further disclose that further detection methods can be carried out on the cells because each cell can be immediately located and its reaction to other detection substances can be recorded (paragraph 0027) which fulfills the specific limitation of claim 10 requiring the identification of a rare event at a “coordinate”. Packman et al disclose that said cells can be further labeled with propidium iodide stain (paragraph 0024) thus fulfilling the specific embodiment of claims 14 and 16 because the combination of propidium iodide with another stain is equivalent to a nuclear stain and a counter stain. Packman et al disclose that morphology of the recorded positive cells can then be determined by hematological staining methods (paragraph 0026) which fulfills the specific embodiments of immunohistochemical staining in claim 13. Packman et al disclose that FISH can be carried out on the isolated cells along with other detection methods (paragraph 0027) which fulfills the specific embodiments of claim 17 because FISH incorporated in situ hybridization. It would have been inherent in the method of Packman et al that the anti-epithelial antibody was selected to avoid cross-reactivity with the beads in order that the antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells.

Claims 1-4, 6-13, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Liberti et al (WO 02/06790).

Liberti et al disclose a method of detecting and isolating tumor cells, virally infected cells, fetal cells in maternal circulation, virus particles, bacterial cells, white blood cells, myocardial cells, epithelial cells, and endothelial cells in body fluids (claims 1, 3 and 6). Liberti et al disclose that cancers cells of epithelial origin can be isolated from patient blood or bone marrow sample by using immunomagnetic particle which bind to cancer cells (claims 2 and 4). Liberti et al teach that the immunomagnetic particles comprise a monoclonal or polyclonal anti-epithelial antibody attached to supermagnetic particles (claim 11), thus fulfilling the specific embodiment of an antibody which fulfills the specific embodiments of claims 6 and 7. Liberti et al disclose the staining of the isolated cells for intracellular antigens (page 49, lines 10-15) which fulfills the specific embodiment of immunohistochemistry which fulfills the specific embodiments of claim 11, 13 and 17. Liberti et al disclose multiparameter flow cytometry, and image analysis (claim 7) which fulfills the specific limitations of claim 10 and 18 requiring a digital image and the association of a rare event with a particular coordinate. Further, it would have been inherent in the method of Liberti et al that the anti-epithelial antibody was selected to avoid cross-reactivity with the beads in order that the antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells. .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) in view of Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265).

O'Hara et al teach the specific limitations of claims 1-4, 6-13, 17 and 18 for the reasons set forth above. O'Hara et al do not specifically teach propidium iodide staining and a counter stain.

Grizwald et al teach the combination of propidium iodide staining as a counter stain to staining with an anti human PSA antibody (page 255 under section 2.12).

It would have been prima facie obvious at the time the claimed invention was made to combining the histological stating of the isolated cancer cells with propidium iodide counter stain. One of skill in the art would have been motivated to do so in order to provide more morphological data regarding the isolated cell population. Because propidium iodide only stains double stranded DNA said stain will provide the nuclear reference point for any other non-nuclear staining in the cell cytoplasm or membrane. One of skill in the art would understand that the nuclear staining with propidium iodide would provide a reference point for further qualification of reactivity with other stains.

Claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) in view of in view of Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265).

Liberti et al teach the specific limitations of claims 1-4, 6-13, 17 and 18 for the reasons set forth above. Liberti et al do not specifically teach propidium iodide staining and a counter stain.

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Grizwald et al teach the combination of propidium iodide staining as a counter stain to staining with an anti human PSA antibody (page 255 under section 2.12).

It would have been prima facie obvious at the time the claimed invention was made to combining the histological staining of the isolated cancer cells with propidium iodide counter stain. One of skill in the art would have been motivated to do so in order to provide more morphological data regarding the isolated cell population. Because propidium iodide only stains double stranded DNA said stain will provide the nuclear reference point for any other non-nuclear staining in the cell cytoplasm or membrane. One of skill in the art would understand that the nuclear staining with propidium iodide would provide a reference point for further qualification of reactivity with other stains.

Claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) and Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265).as applied to claims 1-14 and 16-18 above, and further in view of Singer et al (U.S. 6,323,337).

Claim 14 further includes the stains of YOYO, TOTO and SYTOX. Neither O'Hara et al nor Grizwald et al teach said stains.

Singer et al teach the nucleic acid stains of YOYO, TOTO and SYTOX exhibit enhanced fluorescence when associated with nucleic acids (column 14, lines 28-46).

It would have been prima facie obvious at the time the claimed invention was made to substitute YOYO, TOTO and SYTOX for propidium iodide in the method rendered obvious by the combination of O'Hara et al and Grizwald et al. One of skill in the art would have been motivated to do so by the teachings of Singer et al on the improvement afforded by the use of nucleic acid dyes YOYO, TOTO or SYTOX.

Claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of Singer et al (U.S. 6,323,337).

Claim 14 further includes the stains of YOYO, TOTO and SYTOX. Packman et al does not teach said nucleic acid stains.

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Singer et al teach the nucleic acid stains of YOYO, TOTO and SYTOX exhibit enhanced fluorescence when associated with nucleic acids (column 14, lines 28-46).

It would have been prima facie obvious at the time the claimed invention was made to substitute YOYO, TOTO and SYTOX for propidium iodide in the method of Packman et al. One of skill in the art would have been motivated to do so by the teachings of Singer et al on the improvement afforded by the use of nucleic acid dyes YOYO, TOTO or SYTOX.

Claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) and Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265).as applied to claims 1-14 and 16-18 above, and further in view of Singer et al (U.S. 6,323,337).

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Claims 1-4, 6-15 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) in view of Bloom and Fawcett (A Textbook of Histology, 1962, page 15). Claim 14 embodies the method of claim 13 wherein the dye is selected from a group including hematoxylin. Claim 15 embodies the method of claim 13 wherein the dye is eosin.

O'Hara et al do not specifically teach the dyes of hematoxylin and eosin. Bloom and Fawcett teach that hematoxylin and eosin is the most common histological staining method.

It would have been prima facie obvious at the time the claimed invention was made, to include the dyes hematoxylin and eosin in the method of O'Hara et al. One of skill in the art

would have been motivated to do so by the teachings of Bloom and Fawcett regarding the common use of hematoxylin and eosin. One of skill in the art would know that the use of this combination would enable comparisons with other tumor cells stained by the same combination.

Claims 1-4, 6-15 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of Bloom and Fawcett (A Textbook of Histology, 1962, page 15).

Packman et al do not specifically teach the dyes of hematoxylin and eosin. Bloom and Fawcett teach that hematoxylin and eosin is the most common histological staining method.

It would have been prima facie obvious at the time the claimed invention was made, to include the dyes hematoxylin and eosin in the method of Packman et al. One of skill in the art would have been motivated to do so by the teachings of Bloom and Fawcett regarding the common use of hematoxylin and eosin. One of skill in the art would know that the use of this combination would enable comparisons with other tumor cells stained by the same combination.

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It would have been prima facie obvious at the time the claimed invention was made, to include the dyes hematoxylin and eosin in the method of Liberti et al. One of skill in the art would have been motivated to do so by the teachings of Bloom and Fawcett regarding the common use of hematoxylin and eosin. One of skill in the art would know that the use of this combination would enable comparisons with other tumor cells stained by the same combination.

Claims 1-13, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) in view of Thomas et al (U.S. 6,117,985).

Claim 5 embodies the method of claim 1 wherein the separating is done by negative selection.

O'Hara et al teach the separating by positive selection. O'Hara et al do not teach separating by negative selection.

Thomas el al teach separating non-hematopoietic tumor cells from a sample comprising hematopoietic cells (claims 1-11).

It would have been *prima facie* obvious to use the negative selection method of Thomas et al prior to the positive selection method of O'Hara et al. One of skill in the art would have been motivated to combine the two methods because they are both recognized in the art as method for the isolation of rare tumor cells and it would be expected that both methods would contribute to the isolation of a population of tumor cells.

Claims 1-14, 16, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of Thomas et al (U.S. 6,117,985).

Packman et al teach separating by positive selection rather than by negative selection.

Thomas el al teach separating non-hematopoietic tumor cells from a sample comprising hematopoietic cells (claims 1-11).

It would have been *prima facie* obvious to use the negative selection method of Thomas et al prior to the positive selection method of Packman et al. One of skill in the art would have been motivated to combine the two methods because they are both recognized in the art as method for the isolation of rare tumor cells and it would be expected that both methods would contribute to the isolation of a population of tumor cells.

Claims 1-13, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) in view of Thomas et al (U.S. 6,117,985).

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It would have been *prima facie* obvious to use the negative selection method of Thomas et al prior to the positive selection method of Liberti et al et al. One of skill in the art would have been motivated to combine the two methods because they are both recognized in the art as method for the isolation of rare tumor cells and it would be expected that both methods would contribute to the isolation of a population of tumor cells.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.

6/25/2006



KAREN A. CANELLA PH.D
PRIMARY EXAMINER